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Research in Biotechnology and Environmental Science. 2023; 2(2): 24-29.

DOI: 10.58803/rbes.v2i2.14

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Reveiw Article

Recent Advances in the Prevention and Treatment of Chemotherapy–induced Cardiotoxicity

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ARTICLE INFO

Article History:
Received: 03/03/2023
Accepted: 15/05/2023

Keywords:
Anthracycline
Cancer
Cardiotoxicity
Chemotherapy

ABSTRACT

The current study aimed to overview recent advances in preventing and treating chemotherapy-induced cardiotoxicity. Chemotherapy is widely used in cancer treatment, however, it can have adverse effects on the heart, leading to the development of risk factors, such as hypertension, obesity, dyslipidemia, and metabolic syndrome. Anthracycline compounds are the most commonly used chemotherapy agents and are associated with an increased risk of developing anthracycline-induced cardiotoxicity (AIC). The precise mechanisms underlying AIC remain a subject of debate, but evidence suggests that the primary causes are the generation of reactive oxygen species (ROS) and subsequent oxidative stress. Several risk factors have been linked to the development of AIC, including cumulative dose, pre-existing cardiac disease, age, gender, and cardiac risk factors. Genetic susceptibility may also play a role as a potential risk factor for AIC. In order to protect cardiac function, various strategies have been explored, such as developing less-toxic derivatives of anthracyclines, determining safer cumulative anthracycline doses, and identifying new cardioprotective agents. Prophylactic treatment with cardioprotective agents is the best approach for high-risk patients. This article reviewed the present strategies for protecting cancer patients from AIC based on effective cardioprotective drugs along with the balance between their benefits and potential adverse effects.

1. Introduction

The considerable advances in detecting and treating cancer patients have led to a remarkable increase in life expectancy during the past two decades. Chemotherapy, with anti- cancer effects in the treatment of both solid and hematologic malignancies, significantly contributes to the potential for cancer cure and subsequent improved survival rates. Nevertheless, these therapies are not without their drawbacks, particularly with regard to their impact on cardiac health. Adverse effects on the heart encompass a spectrum of consequences, including the development of multiple risk factors, such as hypertension, obesity, dyslipidemia, and metabolic syndrome. Additionally, there is an increased likelihood of subsequent cardiotoxicity, which may accelerate cardiomyopathy in patients treated with antitumor agents[1,2].

Anthracyclines compounds, including daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone, are the most common chemotherapy agents. These compounds used extensively to remedy different kinds of cancer, such as breast cancer, lymphoma, esophageal carcinoma, sarcoma, small cell carcinoma of the lung, pediatric leukemia, solid tumors[3]. However, caution is required for the clinical usefulness of anthracyclines due to their various adverse effects, especially the development of anthracycline-induced cardiotoxicity (AIC) that increases the risk of developing cardiac dysfunction and impacts the quality of life and mortality of cancer patients. It is estimated that regimens using anthracyclines would increase the risk of developing late-onset heart failure in 5 to 23 percent of patients. Furthermore, this cardiac complication amplifies mortality rates by 5 times. However, the prognosis can be significantly enhanced through early detection and preventive measures[4,5].

Anthracycline-induced cardiotoxicity is thought to arise

► *Cite this paper as*: Kazemian H, Mehrad-Majd H. Recent Advances in the Prevention and Treatment of Chemotherapy–induced Cardiotoxicity. Research in Biotechnology and Environmental Science. 2023; 2(2): 24-29. DOI: 10.58803/rbes.v2i2.14

through a range of mechanisms. These include the inhibition of essential cellular processes such as DNA, RNA, and protein synthesis, as well as interference with DNA repair, replication, and transcription. Additionally, anthracyclines have been shown to generate reactive oxygen species (ROS), which can lead to oxidative stress within cardiac cells. Another proposed mechanism involves the inhibition of topoisomerase II, leading to the initiation of apoptosis. Furthermore, anthracyclines can interfere with DNA strand separation and impede helicase activity. These multifaceted mechanisms collectively contribute to the development of cardiotoxicity associated with anthracycline use[6,7]. Most mechanisms involve the formation of reactive oxygen species (ROS), leading to oxidative stress as the primary cause of anthracycline-induced cardiotoxicity, mediating both death and survival of cardiomyocytes[8]. Recent advances in understanding the pathophysiology of AIC and identification of patient risk factors have led to the exploration of cardio-protective agents and the development of new approaches for the prevention and treatment of patients prone to cardiomyopathy.

Regarding the differences in clinical characteristics and pathophysiology of various types of cancer, and consequently, different responses to anthracycline chemotherapy, it is difficult to define a single strategy to prevent/treat AIC. With this in mind and considering the fact that the AIC may cause irreversible damage to the myocardium, the early detection of cardiotoxicity and developing prevention strategies is a more practical approach than treatment[9]. Extensive efforts have been conducted to monitore, prevent, and treat AIC, ranging from the continuous infusion of anthracycline, use of liposomal drugs or their less cardiotoxic derivative (such as epirubicin or idarubicin), and the concomitant therapy by cardioprotective agents[10]. This paper investigated the present strategies for protecting cancer patients from AIC based on effective cardioprotective drugs and the balance between their benefits and harms.

2. Mechanisms of anthracycline-induced cardiotoxicity

The exact molecular mechanism of AIC remains controversial and is likely to be multifactorial. However, a growing body of evidence has indicated that the generation of ROS and subsequent oxidative stress is the primary cause of AIC. The AIC is a cumulative, dose-dependent phenomenon leading to direct oxidative damage to cellular components, including chromatin and DNA. In the heart, this process manifests as typical pathologic changes, such as swelling and disruption of the mitochondria, vacuolar degeneration of the sarcoplasmic reticulum, and myofilament degeneration and subsequent loss of myocyte[11,12].

Anthracycline-induced generation of ROS can occur through at least two enzymatic and nonenzymatic pathways in cardiomyocytes, leading to cell death through apoptotic pathways[13,14]. Anthracyclines would lead to the reduction of oxygen to form a superoxide anion radical due to interaction with the cardiolipin, a phospholipid located within the inner mitochondrial membrane at the site of the respiratory chain, and other cytochrome-containing enzymes. This situation causes mitochondrial damage, followed by caspase 9 and caspase 3 activation, opening of the mitochondrial permeability transition pore, and the release of cytochrome C into the cytosol and then induction of cell apoptosis[15-17]. In contrast to rapidly dividing cancer cells that the anthracycline-induced DNA damage is the primary mechanism responsible for their killing efficacy, the toxicity in cardiomyocytes is related to free radical formation due to their high reliance on oxidative substrate metabolism, which requires more volume of mitochondria, and therefore they are much more sensitive to the anthracycline-induced oxidative stress even in lower anthracycline concentrations[18].

Anthracycline-induced oxidative stress activates several intracellular pathways consisting of stress-activated protein kinases and mitogen-activated protein kinases. These pathways regulate cellular responses to stimuli, either survival or apoptosis. The balance between those cytotoxic or cytoprotective pathways is determinant in the final cardiomyocytes fate and response to anthracyclines[12,19]. From the molecular point of view, it is also well established that topoisomerase 2β (Top2β) is the principal molecular target of anthracycline's antitumor activity, which modulates DNA topology during replication, recombination, and transcription. Anthracycline-mediated inhibition of Top2β would lead to the accumulation of protein-associated DNA breaks, mitochondrial dysfunction, generation of reactive oxygen species, and induction of apoptosis in treated cells due to irreversible stabilization of the complexes of DNA and Top2β in the cleaved status[20-23]. The development of novel treatments decreasing the toxicity of anthracyclines requires substantial attention to these cytoprotective pathways and molecular issues. On the basis of this molecular insight, new strategies have been developed for changes in cancer treatment protocols and exploring the novel cardioprotective agents against anthracycline chemotherapy.

3. Risk Factors for Cardiotoxicity

The AIC is cumulative and *dose-dependent, which may* range from subtle changes in myocardial strain or biomarkers to subclinical decrements of left ventricular ejection fraction (LVEF) and overt cardiomyopathy[24]. Anthracycline-related cardiac toxicity has been classified as acute onset (within the first week of treatment), early (occurring < 1 year), or late onset (occurring > 1 year) after anthracycline treatment[25]. In contrast to acute-onset toxicity, which occurs in less than 1 % of patients and is a dose-independent, delayed AIC manifest in a dose-dependent fashion. It manifests as a progressive endomyocardial damage rather than a pericarditis-myocarditis syndrome. Due to additional cancer treatment or other cardiovascular risk factors, the majority of patients who develop early-onset toxicity indicate late-

onset cardiomyopathy[26].

Available studies suggest that various clinical risk factors have been linked to the development of AIC. These factors include age >65 years, pre-existing cardiac disease, female gender, and cardiac risk factorsm, cumulative dose[27]. Other conditions like hypertension, hyperlipidemia, concurrent mediastinal radiation, diabetes, and obesity, may also impact cardiotoxicity risk after anthracycline therapy[27].

The AIC is unpredictable in individuals, even with similar cumulative doses and clinical conditions[12]. This suggests that aside from the risk factors listed above, genetic susceptibility may also be a potential risk factor for anthracycline cardiotoxicity, causing a wide variation in an individual's sensitivity to cardiac toxicity. Potential genetic modulators of this sensitivity as well as genes involved in the anthracycline metabolism pathways, have been implicated in cardiotoxicity development[28]. In contrast, several gene variants, including variants in ABCB1, ABCB4, ABCC1, and in the solute SLC28A3 or hCNT3 gene, have also conferred significant protection against AIC[29]. Several studies have recently investigated the prognostic value of genetic variants for early detection of AIC[30-32]. Moreover, a recent systematic review that was published has revealed that genetic variations in genes related to the biochemistry of anthracyclines and the pathways associated with cardiomyopathy could potentially serve as predictors for AIC[33].

4. Strategies for the protection of cardiac function

Besides advances in understanding the exact molecular mechanism underlying AIC, continued efforts have been initiated seeking potential strategies to prevent or treat cardiac complications of cancer chemotherapy. Since anthracyclines improve the life expectancy of patients with cancer, ongoing efforts have been directed toward developing more effective methods for improving early detection of cardiac injury and dysfunction, developing less-toxic derivatives of anthracyclines, determining the safer cumulative anthracycline doses, and finally, identification of new cardioprotective agents as prophylactic treatment. It is of utmost importance to consider opportunities to develop strategies for the primary prevention of cardiotoxicity that protect the heart before it develops clinically evident damage. Despite the lack of universally well-established specific therapies for the prevention or treatment of anthracycline-induced cardiac dysfunction, all proposed preventive approaches during anthracycline treatment are categorized as primary and secondary prevention based on the patient's clinical condition[1,10]. Primary prevention includes all potential strategies in which anthracycline cardiotoxic potency is reduced due to continuous infusion of anthracycline, use of liposomal forms of drugs, or implementation of less-toxic derivatives (such as epirubicin or idarubicin) as well as prophylactic treatment with cardioprotective agents (dexrazoxane) in conjunction with cancer therapy[34-36]. Secondary prevention strategies involve the use of sensitive imaging or cardiac biomarkers to early detection and treatment of left ventricular dysfunction before the development of overt cardiac dysfunction and apply to interventions for high-risk patients with subclinical cardiotoxicity[37-40]. As long as there is no consensus therapy for AIC, evidence suggests that prophylactic treatment with cardioprotective agents is best for high-risk patients. The following section provides an overview of cardioprotective agents with natural or synthetic origins used in conjugation with cancer therapy before it develops clinically evident damage.

5. Cardioprotective agents

5.1. Dexrazoxane

Dexrazoxane is an iron-chelating agent used as a cardioprotective agent in cancer patients undergoing anthracycline chemotherapy. It works by inhibiting the formation of anthracycline-iron complexes that generate free radicals leading to oxidative stress and subsequent cardiotoxicity[41]. Dexrazoxane has been shown to reduce the incidence and severity of AIC without affecting the antitumor efficacy of anthracyclines[42]. A meta-analysis of randomized controlled trials showed that dexrazoxane significantly reduced the risk of developing cardiac dysfunction in patients treated with anthracyclines compared to controls[43]. The American Society of Clinical Oncology recommends the usage of dexrazoxane for patients receiving a cumulative dose of anthracyclines higher than 250 mg/m^2[44].

5.2. Beta-Blockers

Beta-blockers are a group of medications employed in the treatment of hypertension and other cardiovascular diseases. They work by blocking the effects of adrenaline on the heart, reducing the heart rate and blood pressure. In cancer patients undergoing anthracycline chemotherapy, beta-blockers have been shown to have a protective effect against AIC[45]. They reduce the incidence and severity of left ventricular dysfunction and the risk of heart failure and mortality[46]. A meta-analysis of RCTs showed that beta-blockers significantly reduced the risk of progressing cardiac dysfunction in patients treated with anthracyclines, compared to controls[47].

5.3. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors and

Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are a class of drugs used to treat hypertension and other cardiovascular diseases. They inhibit the effects of angiotensin II on the heart and blood vessels, leading to a reduction in blood pressure and enhancement of cardiac function. In cancer patients undergoing anthracycline chemotherapy, ACEIs

and ARBs have been shown to have a protective effect against AIC[48]. They reduce the incidence and severity of left ventricular dysfunction and the risk of heart failure and mortality[49]. A meta-analysis of RCTs reported that ACEIs and ARBs significantly decreased the risk of developing cardiac dysfunction in patients treated with anthracyclines compared to controls[50].

5.4. Statins

Statins are a class of drugs that are employed in the treatment of hyperlipidemia and other cardiovascular diseases. They function by inhibiting the enzyme HMG-CoA reductase, a key enzyme involved in the synthesis of cholesterol synthesis in the liver. In cancer patients undergoing anthracycline chemotherapy, statins have been shown to have a protective effect against AIC[51]. They reduce the incidence and severity of left ventricular dysfunction and the risk of heart failure and mortality[52]. A meta-analysis of RCTs reported that statins significantly reduced the risk of developing cardiac dysfunction in patients treated with anthracyclines compared to controls[53].

5.5. Omega-3 Fatty Acids

Omega-3 fatty acids are a category of polyunsaturated fats present in sources like fish oil and other dietary options. They are known for their anti-inflammatory and antioxidant characteristics, as well as their ability to enhance lipid profiles and endothelial function. In cancer patients undergoing anthracycline chemotherapy, omega-3 fatty acids have been shown to have a protective effect against AIC[54]. They reduce the incidence and severity of left ventricular dysfunction, as well as the risk of heart failure and mortality[55]. A meta-analysis of RCTs showed that omega-3 fatty acids significantly reduced the risk of developing cardiac dysfunction in patients treated with anthracyclines compared to controls[56].

6. Conclusion

Anthracycline-induced cardiotoxicity is a serious complication of anthracycline chemotherapy that can lead to irreversible damage to the myocardium and subsequent morbidity and mortality in cancer patients. The exact molecular mechanism of AIC remains controversial and is likely to be multifactorial, but the generation of ROS and subsequent oxidative stress is the primary cause of AIC. Extensive efforts have been conducted regarding monitoring, prevention, and treatment of AIC, ranging from the continuous infusion of anthracycline, the use of liposomal drugs or their less cardiotoxic derivative, and concomitant therapy by cardioprotective agents. Evidence suggests that prophylactic treatment with cardioprotective agents is the best way to prevent AIC in high-risk patients. Dexrazoxane, beta-blockers, ACEIs and ARBs, statins, and omega-3 fatty acids are among the cardioprotective agents that have been shown to have a protective effect against AIC in cancer patients undergoing anthracycline chemotherapy. However, further studies are required to identify the most effective and safe strategies for preventing and treating AIC in cancer patients.

Declarations

Competing interests

The authors report no conflicts of interest.

Authors' contribution

All authors were involved in data collection, design of the article, interpretation of results, review, and manuscript preparation.

Funding

None.

Ethical considerations

The authors have checked the article for plagiarism, data fabrication, double publication, and redundancy.

Acknowledgments

We would like to express our gratitude to the staff of the Clinical Research Development Unit at Ghaem Hospital, Mashhad University of Medical Sciences, for their assistance in this research. Furthermore, we would like to acknowledge the support received from Mashhad University of Medical Sciences for funding this study, which was conducted as part of a residency thesis (Project No. 961246).

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